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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
FRONDA, CHRISTIAN L	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/727,516	MOLENAAR ET AL.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/892,867.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/05/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' election traverse of Group II, claims 52-64, is acknowledged. The traversal is on the grounds that there is no evidence to show that the claimed product could be used in a materially different process and that a search of all the inventions would not be a serious burden. Applicants arguments filed 06/22/2005 have been acknowledged and found to be persuasive. The restriction requirement has been withdrawn.

2. Claims 44-64 are under consideration in this Office Action.

Claim Objections

3. Claims 47, 52, and 56 objected to because of the following informalities:
Claims 47 and 56 recite the phrase "start codon" twice in the claims which is redundant. Claim 52 should recite "a medium" in line 2. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 44-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is vague and indefinite since the claim recites in parenthesis "(malate dehydrogenase)". It is unclear if the *mdhA* gene encodes this enzyme. It is suggested that the parenthesis be removed and the phrase "which expresses a decreased amount of malate dehydrogenase" be included into the claim. Furthermore, it is suggested that the claims recite "an isolated and modified coryneform bacterium" since the claims recite a comparison to an unmodified starting strain.

Claims 47 and 56 are vague and indefinite because it is not clear that attenuation is achieved by which repressor, activator, operator, promoter, attenuator, ribosme binding site, start codon, and other signal structure. It is unclear whether all of the recited elements are directly linked to *mdhA* or relate to any other gene.

Claims 48 and 57 are vague and indefinite for "attenuated by a modification" since the metes and bounds of the term "modification" is not clear.

Claims 60 and 61 are vague and indefinite since the claims recites in parenthesis "(compared to an unmodified starting strain)". It is unclear if the bacterium actually is to be compared to an unmodified starting strain. It is suggested that the parenthesis be removed .

Claims 59-64 recite the limitation "the process of claim 49". However, claim 49 is a product and not a specific process. There is insufficient antecedent basis for this limitation in the claim. Appropriate correction is requested.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 44-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are genus claims encompassing a genus of coryneform bacteria expressing a decreased amount of malate dehydrogenase, a genus of malate dehydrogenases and polynucleotides encoding malate dehydrogenases, a genus of methods for making any L-amino acids using said coryneform bacteria expressing a decreased amount of malate dehydrogenase,

Each genus is highly variable because a significant number of structural differences

between genus members exists. The scope of the genus of coryneform bacteria expressing a decreased amount of malate dehydrogenase includes many bacteria with widely differing physiochemical properties. The scope of the genus of malate dehydrogenases and polynucleotides encoding malate dehydrogenases includes many malate dehydrogenases and polynucleotides encoding malate dehydrogenases with widely differing amino acid and/or nucleotide sequences along with widely differing structural, chemical, and biophysical properties. The scope of the genus of methods for making any L-amino acids using said coryneform bacteria includes methods for making many amino acids with widely differing physiochemical properties.

The specification discloses a malate dehydrogenase from *Corynebacterium glutamicum* with the amino acid sequence of SEQ ID NO: 3, and the polynucleotide encoding this malate dehydrogenase is disclosed as the nucleotide sequence of SEQ ID NO: 2. The specification discloses an internal, 470 bp long fragment obtained from PCR amplification of the polynucleotide of SEQ ID NO: 2 using primers of SEQ ID NO: 4 and SEQ ID NO: 5. The specification discloses that this 470 bp long fragment was integrated into the genome of *Corynebacterium glutamicum* ATCC 13032 resulting in the inactivation of malate dehydrogenase activity (see Examples 4-5) . Strains of *Corynebacterium glutamicum* having the inactivated malate dehydrogenase identified as MH20-22BmdhA::pEMmdhAint, DG52-5mdhA::pEMmdhAint, and DM58-1mdhA::pEMmdhAint were able to over produce L-lysine compared to wild-type *Corynebacterium glutamicum* strains (see Example 6)

However, neither the specification nor the general knowledge of those skilled in the art provide evidence of any amino acid sequence and nucleotide sequence which would be expected to be common to the members of the claimed genus of malate dehydrogenases and polynucleotides encoding malate dehydrogenases. Furthermore identifying the biological source and name of the enzyme does not provide any structural information of the enzyme and the polynucleotide encoding the enzyme.

The specification does not provide a written description that any other coryneform bacterium that was genetically altered to have a decreased amount of malate dehydrogenase activity, and that such coryneform bacterium is able to produce any L-amino acid. The specification does not provide a written description of any other L-amino acid is produced using the strains identified as MH20-22BmdhA::pEMmdhAint, DG52-5mdhA::pEMmdhAint, and DM58-1mdhA::pEMmdhAint.

In view of the above considerations, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the invention of claims 44-64.

Gene elements which are not particularly described, including regulatory elements and

untranslated regions, are essential to the function of the claimed invention since the claims recite *mdhA, dapA, eno, zwf, pyc, lysE, pck, pgi, and poxB* genes. The art indicates that the structure of genes with regulatory elements and untranslated regions is empirically determined. Therefore, the structure of these elements which applicants considers as being essential to the function of the claims are not conventional in the art.

There is no known or disclosed correlation between the coding region of each gene and the structure of the non-described regulatory elements and untranslated regions of the gene. In view of the above considerations, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of any of the recited *mdhA, dapA, eno, zwf, pyc, lysE, pck, pgi, and poxB* genes.

In regard to claims 47 and 56, the recited repressor gene, activator gene, operator, promoter, attenuator, ribosome binding site, and other signal structure is described by the specification. The art indicates that these elements is empirically determined. Therefore, the structure of these elements which applicants considers as being essential to the function of the claims are not conventional in the art. There is no known or disclosed correlation between the coding region of the *mdhA* gene and the structure of the non-described elements. Thus, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of repressor gene, activator gene, operator, promoter, attenuator, ribosome binding site, and other signal structure of the claimed *mdhA* gene.

8. Claims 44-50, 52-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated modified coryneform bacterium which has an inactivated malate dehydrogenase by integration of a DNA fragment obtained by PCR from SEQ ID NO: 1 using primers of SEQ ID NOs:4 and 5 into the genome of the modified coryneform bacterium, where said malate dehydrogenase of SEQ ID NO: 3 is encoded by the polynucleotide of SEQ ID NO: 1, and a process for making L-lysine using said isolated coryneform bacterium; does not reasonably provide enablement for any isolated modified coryneform bacterium in which the expression of any malate dehydrogenase of any amino acid sequence encoded by any polynucleotide of any nucleotide sequence if inactivated by any method and using such strain for making any L-amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are

summarized In re Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claims encompass any isolated coryneform bacterium expressing any decreased amount of any malate dehydrogenase of any amino acid sequence encoded by any polynucleotide of any nucleotide sequence, and any method for making any L-amino acids using said coryneform bacteria expressing any decreased amount of any malate dehydrogenase.

The specification provides guidance and examples for a malate dehydrogenase from *Corynebacterium glutamicum* with the amino acid sequence of SEQ ID NO: 3, and the polynucleotide encoding this malate dehydrogenase is disclosed as the nucleotide sequence of SEQ ID NO: 2. The specification teaches an internal, 470 bp long fragment obtained from PCR amplification of the polynucleotide of SEQ ID NO: 2 using primers of SEQ ID NO: 4 and SEQ ID NO: 5. The specification shows that this 470 bp long fragment was integrated into the genome of *Corynebacterium glutamicum* ATCC 13032 resulting in the inactivation of malate dehydrogenase activity (see Examples 4-5) . Strains of *Corynebacterium glutamicum* having the inactivated malate dehydrogenase identified as MH20-22BmdhA::pEMmdhAint, DG52-5mdhA::pEMmdhAint, and DM58-1mdhA::pEMmdhAint were able to over produce L-lysine compared to wild-type *Corynebacterium glutamicum* strains (see Example 6). However, the specification does not teach or provide guidance for inactivating said gene or its variants, mutants, or recombinants by an method as well as use of such strains for making any amino acid.

While molecular biological techniques are known in the prior art and the skill of the artisan are well developed, knowledge regarding making any malate dehydrogenase and the nucleotide sequence of the polynucleotide encoding said malate dehydrogenase is lacking along with any procedures to inactivate or alternate the enzyme.

The specification does not provide guidance, prediction, and working examples showing the making any malate dehydrogenase and the nucleotide sequence encoding said malate dehydrogenase followed by any or all methods of attenuation. The specification only shows inactivation of the malate dehydrogenase of SEQ ID NO: 3 in strains of *Corynebacterium glutamicum*, where a 470 bp long fragment obtained from PCR amplification of the polynucleotide of SEQ ID NO: 2 using primers of SEQ ID NO: 4 and SEQ ID NO: 5 is integrated into the genomes of said strains of *Corynebacterium glutamicum*. Furthermore, the specification only shows that strains identified as MH20-22BmdhA::pEMmdhAint, DG52-5mdhA::pEMmdhAint, and DM58-1mdhA::pEMmdhAint over produce L-lysine and no other

amino acid (see Example 6).

Thus, an undue amount of experimentation must be performed to search and screen for strains of bacteria in which any malate dehydrogenase of any amino acid sequence and structure encoded by any polynucleotide is inactivated using the teachings of the specification. Furthermore, an undue amount of experimentation must be performed to search and screen for any type of genetic modification that results in a viable coryneform bacteria that expresses a decreased amount of malate dehydrogenase, and search and screen for any amino acid that can be over produced in the coryneform bacteria compared to an unmodified starting strain. For claims 47 and 56, undue experimentation involving searching and screening for the recited repressor gene, activator gene, operator, promoter, attenuator, ribosome binding site, and other signal structure is required. In regard to claim 60, an undue amount of experimentation is required to search and screen for the specific genetic modification that will result in the enhanced expression of the recited genes. Teaching regarding screening and searching for the claimed invention is not guidance for making the claimed invention. Searching and screening for the claimed invention is outside the realm of routine experimentation.

In view of the above considerations, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.

9. Claim 51 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

For claim 51 it is apparent that plasmid pEMmdhAint is required to practice the claimed invention. As such it must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the requirements of 35 USC § 112, first paragraph, may be satisfied by a deposit of the plasmids.

The process disclosed in the specification to make the plasmid pEMmdhAint does not appear to be repeatable. The nucleotide sequences of the plasmid vectors are not fully disclosed, nor have all the nucleotide sequences required for their construction been shown to be biblically known and freely available. The specification does not disclose a repeatable process to obtain the plasmid and it is not apparent if the nucleotide sequences are readily available to the public. It is not apparent if the source materials to make the plasmid are both known and readily available to the public.

A deposit of the plasmid pEMmdhAint may meet the enablement requirement. If the

deposit is to be made under the terms of the Budapest Treaty, then an affidavit or declaration by the applicant, or a statement by an attorney of record over his/her signature and registration number, stating that the specific microorganism has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809 and MPEP 2402-2411.05, the applicant may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his/her signature and registration number, showing that:

(1) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(2) all restriction upon availability to the public will be irrevocably removed upon granting of the patent;

(3) the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

(4) the deposit will be replaced if it should ever become inviable.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600